HuGE Fact Sheet

Catechol-O-Methyltransferase (COMT) Gene and Breast Cancer

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COMT Gene

The gene for catechol-O-methyltranferase (*COMT*) is located on chromosome 22q11.1-q11.2. It codes for the enzyme *COMT*, which catalyzes the o-methylation inactivation pathway of the major metabolites of estrogen, 2- hydroxyestradiol (2-OHE 2) and 4-hydroxyestradiol (4-OHE 2).

Gene Variants

The *COMT* gene contains a single-nucleotide polymorphism, a G⟶A transition at codon 158. The single-nucleotide transition results in amino acid change, Val⟶Met, which has been linked to decreased methylation activity of the COMT enzyme. The distribution of COMT enzyme activity in the human population has been observed as trimodal: high-activity *COMTH-H*, intermediate-activity *COMTH-L*, and low-activity *COMTL-L*. The frequencies of *COMTH-H*, *H-L*, and *L-L* genotypes were 42%, 45% and 13% respectively for African Americans, whereas for Caucasians, the respective genotype frequencies were 22%, 50%, and 28% respectively based on a case-control study of 645 cases and 642 controls with approximately equal numbers of African American and Caucasian women (1).

Disease Burden

Cumulative lifetime estrogen has been implicated as an important etiological agent in breast carcinogenesis. A possible accumulation of 4-OHE caused by decreased inactivation of catechol estrogen resulting from low COMT activity (COMT *L-L*) has been hypothesized to confer increased risk of breast cancer via oxidative DNA damage.

Several studies provide epidemiologic evidence of the association between breast cancer and polymorphism of the *COMT* gene. A nested case-control study of 112 matched samples in Maryland showed that post-menopausal Caucasian women with the *COMT L-L* genotype and with a body mass index greater than 24 had a greater than three-fold increased risk [OR = 3.85, 95% confidence interval (CI) 1.1-11.5] of developing breast cancer (5). A similar population-based case-control study of 281 cases and 289 community controls in New York confirmed the association between *COMT L-L* and breast cancer risk (more than two-fold increased risk, OR = 2.1, CI 1.4-4.3) only among premenopausal Caucasian women (3). In these two studies, the association between *COMT L-L* and breast cancer was observed only in subgroups. However, the lack of significant association in the total study population could be attributed to small sample size.

A Taiwanese study showed that the low activity of the *COMT L-L* genotype was associated with a four-fold increase (95% CI 1.1-19.1) in post-menopausal breast cancer risk (4). In contrast, two large population-based case-control studies found no significant associations. These two large studies, however, differed from other studies in the source populations. In the first, both cases and controls were drawn from Finland (5). In the second, both cases and controls were drawn from North Carolina, with equal numbers of African American and Caucasian women (1). Other potential differences between study populations were age at menopause and obesity.

Gene-Gene Interactions

Various glutathione S-transferase (GST) isoforms are involved in the inactivation of free radicals that cause oxidative DNA damage. A two-fold increase in breast cancer risk for *GSTM1* null and

the Val-105 Val *GSTP1* genotypes has been observed, suggesting a link between *GST* polymorphisms and breast cancer. One study evaluated the risk of post-menopausal breast cancer associated with a low-activity *COMT* allele stratified by *GST* genotypes. A three- to four-fold increased risk was observed for the combined genotype of *COMT L-L* and *GSTM1* null or *COMT L-L* and Val-105 Val *GSTP1* compared with a two-fold increase in risk for women with the *COMT L-L* genotype alone. This finding suggests a significant gene-gene interaction between the *COMT* and *GST* genes (2). Several other studies did not address the interaction between *COMT* and other genes.

Gene-Environment Interactions

Few studies have evaluated the interactions between *COMT* genotypes and environmental exposure. Since researchers have hypothesized that elevated lifetime exposure to endogenous and/or exogenous estrogen may increase the risk of breast cancer, the interaction between the *COMT L-L* genotype and estrogen exposure was examined in two studies (3,4). For post-menopausal women with the *COMT L-L* genotype, a significantly increased risk of breast cancer was observed in women who had long-term use of estrogen (greater than 30 months), early menarche (before age 12), and post-menopausal obesity. Millikan et al. have also evaluated other gene-environment interactions in which no significant interactions were observed between *COMT* genotypes and physical activity and other markers of estrogen exposure such as smoking and oral contraceptive use (1). Future research studies are needed to evaluate the interaction between the *COMT* genotypes and factors affecting the hormonal milieu of post-menopausal women.

Laboratory Tests

The polymerase chain reaction (PCR) based restriction fragment length polymorphism assay is used to test for of the genetic polymorphisms of *COMT*. PCR is used to amplify a 185 basepair fragment of genomic DNA containing the polymorphism, which is then digested using the *Nla*III restriction enzyme.

Population Testing

Currently, no population-based testing is available to the general public for diagnostic purposes.

References

1. Millikan RC, Pittman GS, Tse CKJ, Duell E, Newman B, Savitz D et al. Catechol-O-methyltransferase and breast cancer risk. *Carcinogenesis* 1998 19:1943-1947.
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4. Huang CS, Chern HD, Chang KJ, Cheung CW, Hsu SM, Shen CY. Breast cancer risk associated with genotype polymorphism of the estrogen-metabolizing genes, CYP 17, CYP1A1, and COMT: a multigenic study on cancer susceptibility. *Cancer Res*.,1999 59:4870-4875.
5. Mitrunen K, Jourenkoa N, Kataja V, Eskelinen M, Kosma VM, Benhamou S et al. Polymorphic catechol-O-methyltransferase gene and breast cancer risk. *Cancer Epid, Biomark & Prevention* 2001 10:635-640.

Web Sites

1. National Alliance of Breast Cancer Organizations
2. National Cancer Institute: Breast Cancer Home Page
3. American Cancer Society Breast Cancer Update